REMARKS

The Office Action of January 2, 2001 presents the examination of claims 44-66. Claims 44-46, and 66 are amended. Claims 67-68 are added. Support for claim 67 is found in Example 8 (last two paragraphs) of the specification. Support for claim 68 is found on page 11, line 23 to page 12, line 14. No new matter is inserted into the application.

Specification

The Examiner objects to the specification for lacking headings. In response to the Examiner's remarks, Applicants amend the specification to add the headings. Thus, the instant objection is overcome.

Claim Objections

The Examiner objects to claims 44 and 45 for missing an "and" between "(c)" and (d)." Applicants amend the claims in accordance with the Examiner's remarks. Thus, the instant objection is overcome.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejects claims 44-65 under 35 U.S.C. § 112,

first paragraph, for allegedly not being described in the specification. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

NEW MATTER REJECTION

On page 3, last two paragraphs of the outstanding Office Action, the Examiner writes:

> *Claims 44-65 encompass "a first inducible promoter" or "a promoter" that is induced by the expression product of the SakR gene.*
>
> *The specification discloses that "the expression of genes under control of the promoter element depicted in Figure 4 is dependent on the expression of the IF-K-R gene cluster (Fig. 1) (page 7, lines 19-21). However, the detailed mechanism of such activation is not described. The specification discloses the expression product of the IF gene that activates the chain of reactions resulting in the production of sakacin P. The specification does not teach the induction of any promoter by the SakR gene expression product per se. The Examiner is unable to locate adequate support in the specification for such claim.*

The Examiner later requires that Applicants cancel "the new matter."

First, the Examiner is incorrect in asserting that a detailed mechanism is not described in the specification. The Examiner's attention is drawn to page 10, lines 24-36, wherein

the activation pathway leading to the expression of a gene of interest is described in detail. Specifically, it is written that the expression product of IF activates the expression product of SakK, which in turn activates the expression product of SakR, and that SakR then activates the expression of the gene of interest. These features of the present invention are recited in the instant claim 44. Thus, the Examiner's assertion that the mechanism of the present invention is not described is unfounded and a rejection based thereon must be withdrawn.

Second, it appears that the Examiner rejects the claims because "a promoter" is allegedly not described in the specification. Applicants respectfully disagree. In claim 44, Applicants claim "a promoter inducible by the activated expression product of the SakR gene or a functional analogue thereof." Thus, Applicants *do not even claim* "any promoter" (i.e., any and all promoters) as asserted by the Examiner. Applicants only claim a promoter inducible by the SakR expression product, or functional analogue thereof, as described in the specification.

In any event, the Examiner appears confused when writing, "there is no indication that a promoter directly inducible by the SakR gene expression product was within the scope of the

invention as conceived by the Applicants…(page 4, first paragraph of the Office Action)." This statement is simply not correct. On page 10, lines 30-33 of the specification, it is written, "The product of R acts on the promoter elements depicted in Fig. 4 either directly, as an activator, or indirectly, by binding to a repressor that until the moment of induction prevents transcription."

Thus, contrary to the Examiner's assertions, the specification indeed discloses that transcription of the gene of interest occurs upon activation by the sakR gene (or functional analogue thereof). As such, the new matter rejection is clearly erroneous and must be withdrawn.

WRITTEN DESCRIPTION

The Examiner rejects claims 44-65 under 35 U.S.C. § 112, first paragraph for allegedly containing subject matter not described in the specification. Specifically, the Examiner maintains her position that a "functional analogue" is not described in the specification. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

On page 4, last paragraph to page 5, first paragraph of the

outstanding Office Action, the Examiner writes:

> *Applicants teach that "[i]n the present invention references to the group IF, K and R (or analogs thereof) should be interpreted as a reference to IF, K, R and such a possible extra gene if it would appear to exist…." Therefore, the claims encompass elements not only not sufficiently described but also not yet discovered at the time the application was filed.*

Applicants are not sure what the Examiner's point is. The claims do not encompass elements not discovered. The Examiner is respectfully requested to point out where in the claims an "undiscovered" element is recited and then Applicants will respond to these allegations if necessary. In any event, Applicants also point out that it is not essential for the mechanism to be completely described in order to make and use an expression system as claimed. For example, other applications have been developed without further knowledge (Axelsson et al. 1998 (FEMS Microbiology Letters 168:137-143); Brurberg et al. 1997 (Molecular Microbiology 26:3478-360)). The fact that SakR binds to the promoter and is essential for activating it has even been confirmed since the filing date of the instant application (Risøen et al., Molecular and General Genetics 224-232 (1999), Molecular Microbiology 37:619-628 (2000), and Molecular Genetics and Genomics 256:198-206(2001)).

On page 5, second paragraph of the outstanding Office Action, the Examiner writes:

> *Applicants disclose IF gene, SakK gene, SakR gene and the promoter of the IF gene of the sakacin P producing Lactobacillus sake LTH673. Therefore, the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. No common structural attributes identify the members of the genus. Given this lack of description of common structural attributes or characteristics that identify members of the genus of an IF gene, a SakK gene or a SakR gene having the requisite properties, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.*

The Examiner continues the same type of argument in asserting that the inducing peptide (i.e. IF and functional analogues thereof) is also not described in the specification (see page 6, second full paragraph):

> *The prior art does not teach and does not allow to predict other members of an IF gene expression product that is not a lantibiotic and is able to induce the production of a bacteriocins.*

Again, the Examiner misinterprets the claims. Applicants do not claim "structural analogues" of the IF, SakK, or SakR genes. In making this rejection, it appears that the Examiner improperly holds the claims of the present invention to the

standard set forth in University of California v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997). In Eli Lilly, the court held that adequate written description of a DNA, including a cDNA, "requires a precise definition, such as by structure, formula, chemical name, or physical properties." The holding in Eli Lilly is not dispositive in the present case because claim 44 is directed to a *gene expression system*, rather than isolated nucleic acids *per se*. In other words, Applicants are claiming "functional analogues" rather than "structural analogues." Several functional characteristics distinguish the "functional analogues" from other genes. For example, in their natural setting they are all involved in the production of bacteriocins, clearly showing the skilled artisan that the invention is directed to lactic acid bacteria rather than other bacteria such as *Staphylococcus aureus*. In naturally occurring lactic acid bacteria, IF genes are located directly upstream of genes encoding a two-component regulatory system. The IF gene or functional analogue thereof encodes a small secreted peptide which, by acting on a Sakk protein or functional analog thereof, activates a cascade resulting in expression of genes involved in bacteriocin production in lactic acid bacteria.

Thus, the skilled artisan would determine the scope of the

claims based on common functional characteristics of the gene expression system, rather than a common amino acid sequence of certain gene products. Written description can be satisfied by description of those common functional characteristics. The Written Description guidelines issued January 5, 2001, 66 F.R. 1099 indicate at page 1106 that adequate written description can be satisfied by disclosure of partial structure, physical and/or chemical properties, functional characteristics **alone**.... In the present instance, Applicants have defined physical, functional properties of the claimed invention in terms of interaction of recited components. It is not necessary for Applicants to provide specific common structural attributes that would identify the members of the genus when the claims recite common functional attributes that identify the members of the genus.

ENABLEMENT

The Examiner rejects claims 44, 46, 48-62, 64, and 65 under 35 U.S.C. § 112, first paragraph for allegedly not being enabled by the specification. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

The Examiner asserts that predictability in the art, guidance in the specification, breadth of the claims, and undue experimentation are pertinent to enablement of the present application. While this is true, Applicants disagree with the manner in which the Examiner considered these factors.

On page 9, last paragraph bridging page 10, first paragraph, the Examiner writes:

> *The following rejection is made over a first inducible promoter of an unknown structure inducible by a SakR gene expression product or by a functional analogue of an IF gene expression product of an unknown structure.*
>
> *The specification teaches one IF gene product that induces its promoter. A functional analogue of a gene product can be a compound of various chemical classes and not necessarily peptides. It is impossible to make a promoter that is inducible by [an] unknown compound. The specification lacks guidance as to what are other compounds in addition to amino acid residues 19-37 of SEQ ID NO:3 that can induce the IF gene promoter.*

Again, the Examiner improperly relies on structural requirements when the skilled artisan only needs functional characteristics to find and use other functional analogues described in the specification. Contrary to the Examiner's assertions, predictability in the art is adequate to produce functional analogues of the present gene expression system, as evidenced by the literature in the art and discussed in prior Replies submitted by Applicants, including: Huehne et al. Microbiology, Vol. 142, pp. 1437-1448, 1996; Nilsen et al., Journal of Bacteriology, Volume 180, pp. 1848-1854, 1998; and Quadri et al., Journal of Bacteriology, Vol. 179, pp. 6163-6171, 1997.

Thus, determination of functional analogues of the instant IF-SakK-SakR genes is well within the skill of the art. Besides using techniques clearly within the knowledge of those skilled in the art, the instant specification clearly directs the skilled artisan on how to find "functional analogues" of the inducing peptide and the SakK and SakR gene products. The Examiner's attention is drawn to the first sentence of Example 3 (page 15) of the specification. There it is written that the repetition of the experiments described in Examples 1 and 2 of the specification led to the identification of a similar mechanism in *L. plantarum* C11. This mechanism, however, was not

known on November 13, 1995. Example 3 shows in that the skilled artisan can use the present invention to find analogous systems in lactic acid bacteria other than LTH673.

For all of the above reasons, Applicants respectfully submit that the term "functional analogue" is adequately enabled by the instant specification. One of ordinary skill in the art could use the guidance of the instant specification to produce functional analogues of the IF-SakK-SakR gene expression system without undue experimentation. As such, Applicants respectfully request that the Examiner withdraw the instant rejection.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 44-65 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Claims 44-63

The Examiner asserts that claims 44-63 are confusing because "they recite a mechanism of action of the expression system and do not distinctly claim the elements included therein." The Examiner clarifies these remarks by stating that, "it is unclear what

compound induces the expression. difference between two sets of genes [sic]." Again, Applicants respectfully disagree.

With regards to the statement "it is unclear what compound induces the expression," claim 44 distinctly states that the expression product of the IF gene, or functional analogue thereof, activates the expression product of the SakK gene, or functional analogue thereof, which in turn activates the expression product of the SakR gene, or functional analogue thereof, which in turn induces the first promoter of the gene of interest causing expression. Thus, the Examiner's comments are unfounded. With regards to the second statement, Applicants cannot even interpret the incomplete statement and thus cannot reply. What difference? What genes? The Examiner is requested to complete the sentence.

As a general note, Applicants point out that the Examiner is not properly applying the standard for definiteness required by 35 U.S.C. § 112, second paragraph. In particular, the Examiner's attention is drawn to MPEP 2106(A)(2)(page 2100-16), wherein it is stated:

> [T]he applicant need not explicitly recite in the claims every feature of the invention. For example, if an applicant indicates that the invention is a particular computer, the claims do not have to recite every element or feature of the computer.

Applicants recite this passage of the MPEP to make the point that the Examiner has no statutory right to demand inherent features of the expression system to be recited in the claims. The claims function to set forth the subject matter which the applicant regards as the invention, which is clearly done in the present case. As such, the rejection made under 35 U.S.C. § 112, second paragraph is improper and should be withdrawn.

Claim 65

The Examiner asserts that claim 65 is unclear for reciting "-10 region," which the Examiner asserts could mean "many regions." Applicants respectfully disagree. This statement is simply not accurate. It is well known in the art that in the context of promoters, nucleotides are numbered positively after (=downstream from) the transcription initiation start site and negatively before (=upstream from) the initiation start site. Thus, -10 simply refers to 10 nucleotides before (=upstream from) the transcription initiation start site. This terminology is common for bacterial genes as evidenced by its use in several textbooks including Genes VI by B. Lewin (Oxford University Press, 1997) page 303; and Biochemistry by C.K. Matthews et al. (Benjamin Cummings/Addison Wesley Longman 2000) page 993.

The Examiner further mentions that the phrase "the expression product of an IF gene is defined as not a lantibiotic" excludes that which "the inventors did not invent rather than distinctly and particularly pointing out what they did invent." In making this rejection, the Examiner refers to MPEP 2173.05(i). It is requested that the Examiner carefully read *all of* said passage. The first sentence of the passage states:

> The current view of the courts is that there is nothing inherently ambiguous or uncertain about a negative limitation. So long as the boundaries of the patent protection sought are set forth definitely, albeit negatively, the claim complies with the requirements of 35 U.S.C. § 112, second paragraph.

The passage does later state that "some older cases were critical of negative limitations," including In re Schecter, 205 F.2d 185 (CCPA 1953), apparently the case upon which the Examiner relies. However, as stated above, this case is no longer good law. The Examiner has no legal or factual basis to rely on this case in making this rejection. As such, the instant rejection is improper and should be withdrawn.

Claim 46

The Examiner asserts that claim 46 is confusing for

reciting "a functional analogue of an expression product of an IF gene comprising residues 19-37 of SEQ ID NO:3..." In response to the Examiner's remarks, Applicants amend claim 46 to delete reference to a functional analogue. Thus, the instant rejection is overcome.

Functional Analogues

It appears that the Examiner rejects all claims for reciting functional analogues when "there is no art-accepted definition of said term." Why does the Examiner insist on an art-accepted definition? The Examiner's attention is again drawn to MPEP 2106(A)(2)(page 2100-16), wherein it is stated:

> ...the definiteness of the language must be analyzed, not in a vacuum, but always in light of the teachings of the disclosure as would be interpreted by one of ordinary skill in the art.

The specification of pages 12-14 clearly teaches the skilled artisan that functional analogues of SakK and SakR can be easily recognized by sequence homology. The cognate analogue of IF can be found by analyzing the DNA upstream of SakK. Again, as evidence that such experimentation is routine in the art, Applicants draw the Examiner's attention to the following publications: Axelsson et al. 1998 (FEMS Microbiology Letters

168:137-143); Brurberg et al. 1997 (Molecular Microbiology 26:3478-360); Risøen et al., (Molecular and General Genetics 224-232 (1999), Molecular Microbiology 37:619-628 (2000), and Molecular Genetics and Genomics 256:198-206(2001)).

For these reasons, the term "functional analogue" is described in the specification as required by statute. The Examiner has no legal basis for asserting that the term must have a wide-spread "art-accepted definition." Thus, the instant rejection is improper and should be withdrawn.

Applicants respectfully submit that all of the present claims are in compliance with 35 U.S.C. § 112, second paragraph. Withdrawal of the instant rejection is therefore requested.

Issues under 35 U.S.C. § 102

The Examiner rejects claims 44-66 under 35 U.S.C. § 102(b) for allegedly being anticipated by Diep et al. (1994), Tichaczek et al. (1994), Axelsson et al., Venema et al. (1994), and Balaban et al. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

During an interview held with the Examiner and the Inventor, the Examiner conceded that the present invention

distinct from Diep et al. in that Diep et al. does not teach anything about (1) the presence of a regulatory mechanism, (2) the character of such mechanisms, (3) the presence or character of an "inducing substance" (i.e. no regulatory signal is revealed) and (4) possible applications, although the genes are co-transcribed from a common promoter.

Further, Diep et al. fails to teach that bacteriocin production by the disclosed lactic acid bacterium is inducible (i.e., regulated) or that plantaricin (encoded by PlnA) is the inducing factor. The function and the application potential of the sequences described therein were not appreciated. Further, putative promoter sequences were assigned incorrectly and the existence of sequence elements with regulatory function was not shown nor appreciated. For these reasons, Applicants respectfully submit that the instant claims are novel and unobvious over the cited prior art references, and respectfully request that the Examiner allow the instant claims.

Tichaczek et al. also fails to teach the inducibility of sakacin P. In the same manner, Axelsson et al. does not show nor state that the promoter is inducible by its gene expression product. Thus, neither Tichaczek et al. nor Axelsson et al. discloses or makes obvious a gene expression system, as

currently claimed. Venema et al. also fails to show the inducibility of sakacin P. Further, there is no indication whatsoever that the promoter preceding the PedABCD cluster is inducible. Applicants stress that even if the genes producing pediocin are "transcribed from a common promoter," this does *not* imply that expression is regulated or that the promoter is inducible. Applicants also make note that the genes in the PedABCD cluster all have a different character than the genes in the PlnABCD operon. It is only mere coincidence that both use the same letters in their respective names. For example, PedA is a bacteriocin, whereas PlnA primarily has a regulatory (inducing) function that was not known prior to the instant filing date.

In summary, neither Tichaczek et al., Axelsson et al., or Venema et al., show, state, or suggest any of the following: (1) the presence of a regulatory mechanism, (2) the character of such mechanism, (3) the presence or character of an "inducing substance" (i.e., no regulatory signal is revealed) and (4) possible applications. None of these authors recognize the instant promoter elements that the present Inventors have found play a role in the regulation of bacteriocin production. Further, even the annotations of promoters of the published

sequences are wrong.

Balaban et al. teaches the production of exoproteins in *Staphylococcus aureus*. *Staphylococcus aureus* is not a lactic acid bacterium; further it is not even a food grade bacterium. *Staphylococcus aureus* is actually a human pathogen. Most importantly, Balaban et al. does not reveal the character of the inducing substance, nor the genetic organization of its gene. Further details of the *Staphylococcus aureus* system were not revealed until a December 1995 paper authored by Ji et al. (PNAS USA, 92:12055-12059) was published. However, this publication still failed in reveal an inducible promoter.

For all of the above reasons, Applicants respectfully submit that the present invention is neither anticipated nor obvious over the cited prior art references. Applicants respectfully request that the Examiner withdraw the instant rejection.

Applicants respectfully submit that all of the present claims define patentable subject matter such that this application should be placed into condition for allowance. Early and favorable action of the merits of the present application is respectfully requested.

Should there be any outstanding matters that need to be

resolved in the present application, the Examiner is respectfully requested to contact Kristi L. Rupert, Ph.D. (Reg. No. 45,702) at the telephone number below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to the provisions of 37 C.F.R. § 1.17 and 1.136(a), Applicants hereby petition for an extension of three (3) months to July 2, 2001 for the period in which to file a response to the outstanding Office Action. The required fee of $890.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and further replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fee required under 37 C.F.R. 1.16 or under 37 C.F.R. 1.17; particularly, extension of time fees.

Respectfully yours,

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VERSION SHOWING MARKED-UP CLAIMS

IN THE SPECIFICATION

The specification is amended to insert headings.

IN THE CLAIMS

The claims are amended as follows:

44. A gene expression system comprising

(1) an operon comprising:

(a) an IF gene, or a functional analogue thereof;

(b) a SakK gene, or a functional analogue thereof;

(c) a SakR gene, or a functional analogue thereof; and

(2)[(d)] a vector comprising a cloned polynucleotide of interest linked to a first inducible promoter,

wherein in said gene expression system, the expression product of the IF gene, or functional analogue thereof, activates the expression product of the SakK gene, or functional analogue thereof, and

the activated expression product of the SakK gene, or functional analogue thereof, activates the expression product of the SakR gene, or functional analogue thereof, and

the activated expression product of the SakR gene, or functional analogue thereof, induces the first promoter of the gene of interest,

thereby causing expression of the gene of interest; and

wherein said SakK gene and said SakR gene are co-transcribed; and

wherein the expression product of said IF gene or functional analogue thereof is

(a) identical or similar to peptides that are naturally produced by lactic acid bacteria and are capable of inducing the production of bacteriocins by said lactic acid bacteria,

(b) not a lantibiotic, and

(c) induces the expression of genes involved in bacteriocin production in lactic acid bacteria.

45. A gene expression system comprising:

(1) an operon comprising

(a) an IF gene;

(b) a SakK gene;

(c) a SakR gene; and

(2) [(d)] a vector comprising a cloned polynucleotide of interest linked to a first inducible promoter,

wherein in said gene expression system, the expression product of the IF gene activates the expression product of the SakK gene, and

the activated expression product of the SakK gene activates the expression product of the SakR gene and

the activated expression product of the SakR gene induces the first promoter of the gene of interest,

thereby causing expression of the gene of interest; and

wherein said SakK gene and said SakR gene are co-transcribed; and

wherein said the expression product of said IF gene is

(a) identical or similar to peptides that are naturally produced by lactic acid bacteria and are capable of inducing the production of bacteriocins by said lactic acid bacteria,

(b) not a lantibiotic, and

(c) induces the expression of genes involved in bacteriocin production in lactic acid bacteria.

46. (Amended) The gene expression system of claim 44, wherein said expression product of the IF gene[, or a functional analogue thereof] comprises the sequence of residues 19-37 of SEQ ID NO:3.

65. (Amended) An isolated nucleic acid comprising:

two repeated nucleotide sequences 5 to 10 nucleotides long and spaced 17 to 23 nucleotides apart, wherein the downstream member of said repeated sequence is located 30 to 38 nucleotides upstream [downstream] from a -10 region of a bacterial gene,

wherein said isolated nucleic acid promotes transcription of an operatively linked coding nucleic acid sequence which is activated by an expression product of a SakR gene or functional analog thereof that has been activated by an expression product of a SakK gene or functional analog thereof.

66. (Amended) The isolated nucleic acid of claim 65, wherein said repeated nucleotide sequences are selected from the group consisting of residues 7-14 and 30-38 of SEQ ID NO:6, residues 7-14 and 30-38 of SEQ ID NO:7, residues 7-14 and 30-38 of SEQ ID NO:8, residues 7-14 and 31-38 of SEQ ID NO:9, and residues 7-8, 10-14 and 31-38 of SEQ ID NO:10 [, residues 6-7, 9-17 and 32-36 of SEQ ID NO:11, and residues 6-7, 9-17 and 32-36 of SEQ ID NO:12].